

**We claim:**

- 1 1. A process for the production of atorvastatin calcium in amorphous form comprising:
  - 3 a) reacting a solution of (*4R*-*cis*)-1,1-dimethylethyl-6-{2-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1*H*-pyrrol-1yl]ethyl}-2,2-dimethyl-1,3-dioxane-4-acetate (Compound H) in a water-miscible solvent with an acid to obtain [*R*-(*R*<sup>\*</sup>,*R*<sup>\*</sup>)]-1,1-dimethylethyl-2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1*H*-pyrrole-1-heptanoate (Compound I);
  - 9 b) treating Compound I with an alkali metal hydroxide to obtain an alkali metal salt of atorvastatin;
  - 11 c) washing the solution of alkali metal salt of atorvastatin with a solvent immiscible or slightly miscible in water;
  - 13 d) treating the washed solution of alkali metal salt of atorvastatin with a calcium salt or calcium hydroxide to obtain atorvastatin calcium;
  - 15 e) isolating crude atorvastatin calcium;
  - 16 f) purifying crude atorvastatin calcium by dissolving in a mixture of tetrahydrofuran and methanol, and precipitating with water to obtain pure atorvastatin calcium in crystalline form; and
  - 19 g) converting crystalline pure atorvastatin calcium so obtained into amorphous form.
- 1 2. A process for purifying atorvastatin calcium comprising dissolving crude atorvastatin calcium in a mixture of tetrahydrofuran and methanol, and precipitating with water to obtain pure atorvastatin calcium in crystalline form.
- 1 3. The process of claim 2, wherein the acid used is an inorganic acid.

- 1    4. The process of claim 3, wherein the acid is selected from the group consisting of  
2       hydrochloric, hydrobromic, sulphuric, phosphoric and nitric acids.
- 1    5. The process of claim 1, wherein the water-miscible solvent is selected from the  
2       group consisting of acetonitrile, alcohols, cyclic ethers, ketones and mixtures  
3       thereof.
- 1    6. The process of claim 5, wherein alcohols are selected from the group consisting of  
2       methanol, ethanol, propanol, and isopropanol.
- 1    7. The process of claim 1, wherein the reaction of step b) is carried out at a pH of  
2       about 12.
- 1    8. The process of claim 1, wherein the alkali metal hydroxide is selected from the  
2       group consisting of sodium hydroxide, potassium hydroxide and lithium  
3       hydroxide.
- 1    9. The process of claim 1, wherein the solvent immiscible or slightly miscible in  
2       water is selected from the group consisting of ethers, esters, and hydrocarbons.
- 1    10. The process of claim 9, wherein ethers are selected from the group consisting of  
2       methyl tertiary butyl ether, diethyl ether, methyl ethyl ether and dibutyl ether.
- 1    11. The process of claim 1, wherein the pH of the solution of step c) is lowered to  
2       about 7.8 to 8.2 with an acid before proceeding with step d).
- 1    12. The process of claim 1, wherein step d) is performed at a temperature of about 45  
2       to 55 °C.
- 1    13. The process of claim 1, wherein the calcium salt is selected from the group  
2       consisting of calcium acetate, calcium chloride, calcium sulfate, calcium nitrate  
3       and calcium phosphate.
- 1    14. The process of claim 1, wherein any residual solvent immiscible or slightly  
2       miscible in water remaining in the reaction mixture is removed after step d) is  
3       removed under reduced pressure.
- 1    15. The process of claim 1, wherein crude atorvastatin calcium is precipitated by  
2       addition of water.

- 1    16. The process of claim 15, wherein water is added at a temperature of about 55 to  
2        65°C.
- 1    17. The process of claim 1, 15 or 16, wherein seeds of crystalline atorvastatin calcium  
2        are added to the reaction mixture.
- 1    18. The process of claim 1, or 15 to 17, wherein crude atorvastatin calcium is isolated  
2        by cooling the reaction mixture to a temperature of about 20 to 35 °C.
- 1    19. The process of claim 1 or 2, wherein tetrahydrofuran, methanol and water are in  
2        the volume ratio 1:1:4.
- 1    20. The process of claim 1, 2 or 19, wherein water is added at a temperature of about  
2        60 to 65 °C.
- 1    21. The process of claims 1, 2, 19 or 20, wherein seeds of crystalline atorvastatin  
2        calcium are added to facilitate the precipitation.
- 1    22. The process of claim 21, wherein seeds of crystalline atorvastatin calcium are  
2        added at a temperature of about 50 °C.
- 1    23. The process of claims 1, or 19 to 22, wherein pure atorvastatin calcium is isolated  
2        by cooling the mixture to a temperature of about 30 to 35 °C.
- 1    24. The process of claim 1, which comprises an additional step wherein the pure  
2        crystalline atorvastatin calcium obtained after step f) is suspended in a mixture of  
3        methanol and water in the volume ratio 1 to 5 and stirred with seed crystals of  
4        crystalline form I, to obtain atorvastatin calcium in crystalline form I.
- 1    25. The process of claim 24, wherein the stirring is performed at a temperature of  
2        about 30 to 45°C.
- 1    26. The process of claim 1, which comprises an additional step wherein the pure  
2        crystalline atorvastatin calcium obtained after step f) is suspended in 15 to 25  
3        volumes (w.r.t weight of atorvastatin calcium) of a mixture of methanol and water  
4        in the volume ratio 3 to 2 and stirred with seed crystals of crystalline form II, to  
5        obtain atorvastatin calcium in crystalline form II.

- 1    27. The process of claim 24, which comprises a further additional step wherein the  
2       obtained crystalline form I of atorvastatin calcium is suspended in 15 to 25  
3       volumes (w.r.t weight of atorvastatin calcium) of a mixture of methanol and water  
4       in the volume ratio 3 to 2 and stirred with seed crystals of crystalline form II, to  
5       obtain atorvastatin calcium in crystalline form II.
- 1    28. The process of claim 26 or 27, wherein the stirring is performed at a temperature of  
2       about 10 to 65 °C.
- 1    29. The process of claim 1, wherein amorphous atorvastatin calcium is obtained by  
2       dissolving pure crystalline atorvastatin calcium in tetrahydrofuran and adding the  
3       resulting solution to cyclohexane.
- 1    30. The process of claim 29, wherein water is added to tetrahydrofuran to dissolve  
2       pure crystalline atorvastatin calcium.
- 1    31. A process for the production of stabilized, amorphous atorvastatin calcium  
2       comprising:
  - 3       a) dissolving crystalline atorvastatin calcium and an antioxidant in a solvent;
  - 4       b) adding the atorvastatin calcium and antioxidant solution to an antisolvent;  
5       and
  - 6       c) separating precipitated, amorphous atorvastatin calcium from the resulting  
7       suspension to obtain stabilized, amorphous atorvastatin calcium.
- 1    32. A process for the production of atorvastatin calcium in amorphous form  
2       comprising:
  - 3       a) dissolving crystalline atorvastatin calcium in a hydroxylic solvent;
  - 4       b) adding the obtained solution of atorvastatin calcium to a non-hydroxylic  
5       anti-solvent, wherein the non-hydroxylic anti-solvent has a higher boiling  
6       point than the hydroxylic solvent;
  - 7       c) concentrating the solution so obtained to remove the hydroxylic solvent;  
8       and
  - 9       d) separating precipitated amorphous atorvastatin calcium from the resulting  
10      suspension to obtain amorphous atorvastatin calcium.

- 1    33. The process of claim 32, wherein an antioxidant is added to the solution of  
2        atorvastatin calcium in hydroxylic solvent.
- 1    34. The process of claim 31 or 33, wherein the antioxidant is selected from the group  
2        consisting of butylated hydroxyanisole, butylated hydroxytoluene and tertiary-  
3        butylated hydroquinone.
- 1    35. The process of claim 1, wherein the conversion to amorphous form is achieved  
2        according to the process of claim 31, 32 or 33.
- 1    36. The process of claim 30 to 33, wherein the solution of atorvastatin calcium is dried  
2        before precipitation of amorphous atorvastatin calcium.
- 1    37. The process of claim 36, wherein the solution is filtered through dry molecular  
2        sieves.
- 1    38. The process of claim 36, wherein the solution is made using excess of solvent,  
2        which is then concentrated to achieve drying.
- 1    39. The process of claim 31, wherein the solvent is selected from the group consisting  
2        of ketones, esters, chlorinated hydrocarbons, cyclic ethers, alcohols, nitriles,  
3        dipolar aprotic solvents, and mixtures thereof with water.
- 1    40. The process of claim 39, wherein the cyclic ethers are selected from the group  
2        consisting of dioxan, tetrahydrofuran, and mixtures thereof.
- 1    41. The process of claim 31, wherein the anti-solvent is selected from the group  
2        consisting of hydrocarbons and dialkyl ethers.
- 1    42. The process of claim 32, wherein the hydroxylic solvent is selected from the group  
2        consisting of alcohols, and mixtures thereof with water.
- 1    43. The process of claim 39 or 42, wherein alcohols are selected from the group  
2        consisting of methanol, ethanol, propanol, and isopropanol.
- 1    44. The process of claim 32, wherein the non-hydroxylic anti-solvent is selected from  
2        the group consisting of hydrocarbons and dialkyl ethers.
- 1    45. The process of claim 41 or 44, wherein the hydrocarbons are selected from the  
2        group consisting of cyclohexane, hexane, heptane, petroleum ethers, toluene, and  
3        xylene.

1    46. The process of claim 1, wherein (*4R-cis*)-1,1-dimethylethyl-6-{2-[2-(4-  
2    fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1*H*-pyrrol-  
3    1yl]ethyl}-2,2-dimethyl-1,3-dioxane-4-acetate (Compound H) is obtained by  
4    a)    treating (*R*)-ethyl 4-cyano-3-hydroxybutanoate (Compound A) with 1,1-  
5    dimethylethylacetate (Compound B), in the presence of n-butyl lithium and  
6    diisopropyl amine to obtain (*R*)-1,1-dimethylethyl-6-cyano-5-hydroxy-3-  
7    oxohexanoate (Compound C),  
8    b)    treating Compound C with diethyl methoxyborane and sodium borohydride  
9    to obtain [*R*-(*R*<sup>\*</sup>,*R*<sup>\*</sup>)]-1,1-dimethylethyl-6-cyano-3,5-dihydroxyhexanoate  
10   (Compound D),  
11   c)    treating Compound D with 2,2-dimethoxy propane and methanesulfonic  
12   acid to obtain (*4R-cis*)-1,1-dimethylethyl-[6-cyanomethyl-2,2-dimethyl-1,3-  
13   dioxan]-4-acetate (Compound E),  
14   d)    treating Compound E under reducing conditions to obtain (*4R-cis*)-1,1-  
15   dimethylethyl-[6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl] acetate  
16   (Compound F), and  
17   e)    condensing Compound F with ( $\pm$ )-4-fluoro- $\alpha$ -(2-methyl-1-oxopropyl)- $\gamma$ -  
18   oxo-*N*, $\beta$ -diphenylbenzenebutaneamide (Compound G) to obtain (*4R-cis*)-1,1-  
19   dimethylethyl-6-{2-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-  
20   (phenylamino)carbonyl]-1*H*-pyrrol-1yl]ethyl}-2,2-dimethyl-1,3-dioxane-4-acetate  
21   (Compound H).  
1    47. A process for the production of atorvastatin calcium in amorphous form, as herein  
2    described and exemplified by the examples.